REMARKS

The Claim Amendments

Claims 272, 273, 280-284, and 291 were pending in the application and were examined. Claims 272, 273, 280-284, and 291 stand rejected. Claims 272, 273, 280-284, and 291 stand amended in the present Amendment.

Support for the amendments is found, for example, at pages 63-64; at pages 116-117; at pages 162-164; in the claims, and elsewhere in the application as originally filed.

These amendments are made without acquiescence to any rejections, and without prejudice to the prosecution of canceled subject matter in related divisional, continuation, and continuation-in-part applications.

No new matter is added by way of the claim amendments.

The Withdrawn Claim Objections and Rejections

Applicants note the withdrawal of the previous objections to claims 272 and 273, and the withdrawal of the previous rejections under 35 U.S.C. § 112, first and second paragraphs, to claims 272, 273, 280-284, and 291 by the USPTO (pages 3 and 5-6 of the Office Action mailed April 4, 2011).

The Rejections of Claims 281, 282, and 284 under 35 U.S.C. § 112, second paragraph

Claims 281, 282, and 284 stand rejected as allegedly indefinite, the USPTO stating that "[a] broad range or limitation together with a narrow range that falls within the broad range or limitation (in the same claim) is considered indefinite" (page 4 of the instant Office action), and objecting to the phrase "consistent with." However, as amended, none of claims 281, 282, and 284 recite the phrase "consistent with," all claims are directed to retinal abnormalities, and the claims are believed to be definite.

Accordingly, Applicants submit that the rejections of claims 281, 282, and 284 under 35 U.S.C. § 112, second paragraph are overcome.

The Rejections of Claims 272, 273, 280-284, and 291 under 35 U.S.C. § 112, first paragraph

Claims 272, 273, 280-284, and 291 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement, the USPTO suggesting that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The enablement requirement of 35 U.S.C. § 112, first paragraph requires that the specification enable "those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation'." Genentech, Inc. v. Novo Nordisk, A/S 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)).

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). These factors include: "(1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Applicants respectfully traverse the objections to the claims and the rejections to the claims.

The Application is Enabling for PRO224 Knockout Mice Having Retinal Abnormalities

Applicants note the USPTO's acknowledgement that the specification is "enabling for a method of identifying an agent that modulates an eye abnormality, the method comprising: (a) providing a transgenic mouse whose genome comprises a knockout of the gene which encodes for the native sequence PRO224 polypeptide; (b) measuring a physiological characteristic of an eye of the transgenic mouse of (a), wherein the transgenic mouse exhibits the following physiological

characteristic compared with gender-matched wild-type littermates: an increased mean artery-to-vein ratio in the retinas; (c) administering a test agent to the transgenic mouse of (a); and (d) determining whether the test agent modulates said increased mean artery-to-vein ratio in the retinas of the transgenic mouse, whereby an agent which is determined to modulate said increased mean artery-to-vein ratio in the retinas of the transgenic mouse is identified" (pages 7-8 of the instant Office action, emphasis in the original). Applicants further note the USPTO's apparent acknowledgement that the specification is enabling for "a knockout of the gene which encodes for the native sequence PRO224 polypeptide" and for "an increased mean artery-to-vein ratio in the retinas" (page 13, lines 18-21).

The USPTO also states that "[t]he basis of this scope of enablement rejection is that (1) a disruption of a gene encompasses any frame-shift mutation, any in-frame addition, deletion, and any truncation that do not result in complete loss of gene function (i.e. knockout), and (2) the increased mean artery-to-vein ratio in the retinas is the only disclosed physiological characteristic of eye abnormalities exhibited by the DNA33221-1133 (+/-) and (-/-) knockout mouse (notes: mouse DNA33221-1133 gene encoding PRO224 polypeptides)" (page 8, lines 9-14). This USPTO statement regarding the rejections thus acknowledges that DNA33221-1133 (+/-) and (-/-) knockout mice (lacking the gene encoding PRO224 polypeptides) indeed do exhibit retinal abnormalities.

As amended, the claimed methods require the use of a PRO224 knockout transgenic mouse comprising a retinal abnormality resulting from the PRO224 gene knockout. The disclosure of the specification teaches such mice, as acknowledged by the USPTO (see above).

In particular, the application teaches the nucleotide and amino acid sequences of PRO224 molecules (see, e.g., page 46 and Figures 1 and 2) and identifies a cDNA clone that has been deposited with ATCC (ATCC 209263, deposited September 16, 1997 (see page 145, line 16)). The application provides detailed teaching regarding producing transgenic mice having a disruption in a gene encoding for PRO224 polypeptide, and explicit examples of such transgenic mice (see, for example, page 116, line 21 to page 117, line 21; page 146, line 7 to page 147, line 11; page 163, line 14 to page165, line 14; and elsewhere in the application). Thus, particular sequences, SEQ ID NO: 1 and SEQ ID NO: 2, are disclosed in the application. In addition, Applicants note that the methods recite transgenic mice comprising a knockout of the gene that encodes for a native sequence PRO224

polypeptide, which sequences are provided; that the claimed methods require knock-out mice with a phenotype comprising a retinal abnormality, as disclosed in the application; and that methods for generating such knock-out mice, and for measuring retinal abnormalities, are also taught in the application. Thus, Applicants submit that the teaching of the application is detailed and specific, and is sufficient to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation.

Accordingly, claims 272, 273, 280-284, and 291 being directed to methods requiring the use of transgenic PRO224 knockout mice comprising a retinal abnormality resulting from the gene knockout, in view of the specific teaching of the disclosure, and in view of the acknowledgement by the USPTO that the specification is enabling for PRO224 knockout mice having a retinal abnormality (at, for example, pages 7-8, and 13 of the instant Office action), Applicants respectfully submit that the rejections of claims 272, 273, 280-284, and 291 are overcome.

The Application is Enabling for Methods for Identifying an Agent that Modulates a Phenotype

The USPTO suggests that allegedly "the claimed methods require 'identifying an agent that modulates a phenotype associated with disruption of the gene that encodes for a PRO224'" and then suggests that allegedly "the specification does not provide any information regarding any agent that can reverse/modulate the increased mean artery-to-vein ratio" (page 12, lines 11-14 of the instant Office action). However, Applicants respectfully note that the present methods, which require the use of a PRO224 knockout transgenic mouse having a retinal abnormality resulting from the gene PRO224 knockout, are directed to *"identifying an agent that modulates a retinal abnormality"*: the outcome of the practice of the claimed methods is the identification of such an agent; the present claims are not directed to such agents themselves. The claimed methods are indeed enabled by the disclosure of the specification, as discussed above: the disclosure provides PRO224, knockout mice lacking PRO224, retinal abnormalities resulting from the knockout of PRO224, and methods for measuring retinal abnormalities. Thus, the disclosure of the specification teaches one of ordinary skill in the art how to practice the invention without undue experimentation.

Accordingly, for this reason as well, Applicants respectfully submit that the rejections of claims 272, 273, 280-284, and 291 are overcome.

Association Between Retinal Abnormality Phenotype and Physiological Characteristics

The USPTO also suggests that allegedly "there is no clear association, as Applicant asserts, between a phenotype of retinal abnormality (retinal degeneration) and a physiological characteristic of increased mean artery-to-vein ratio" (page 12, lines 17-19 of the instant Office action). Applicants respectfully disagree.

The disclosed measurements of artery and vein dimensions or properties in the retina are themselves retinal abnormalities, since the retinas of the knock-out mice differ from those of wild-type mice. Moreover, the scientific literature indicates that such retinal abnormalities are useful indicators of retinal and other disease states. For example, such measurements may be diagnostic and/or prognostic of hypertension, hyperglycemia, cerebral hypoxia, vascular endothelial dysfunction, and other disorders linked to diabetic retinopathy, macular degeneration, glaucoma, and other retinal abnormalities and disorders. Thus, Applicants believe the USPTO's concerns regarding an alleged lack of association between a phenotype of retinal abnormality and a physiological characteristic of increased mean artery-to-vein ratio are overcome.

Accordingly, Applicants respectfully submit that the rejections of claims 272, 273, 280-284, and 291 are overcome.

PRO224 Knockout Mice Having a Retinal Abnormality Resulting from the Knockout are Predictable

The USPTO suggests that allegedly "the phenotype of transgenic mouse is unpredictable" citing Matthaei and others (pages 14-15, particularly page 14, lines 19-20 of the instant Office Action). However, Applicants note that the present claims, as amended, require a PRO224 gene knockout, instead of the disruption of a gene encoding for PRO224 that was objected to by the USPTO. Moreover, the present claims require that the PRO224 knockout mice used in the claimed methods comprise "a retinal abnormality resulting from the gene knockout." Thus, since the present claims recite that the transgenic mice used in the claimed methods comprise a knockout of the gene encoding for PRO224, and that the gene knockout result in a retinal abnormality, Applicants respectfully submit that any concern regarding an allegedly unpredictable phenotype is believed to be moot. Accordingly, Applicants submit that the concerns regarding subjects discussed by Matthaei are overcome.

Applicants submit that the claimed methods are enabled by the specification, which provides detailed and specific disclosure regarding the gene encoding for PRO224, transgenic mice comprising a knockout the gene encoding for PRO224, retinal abnormalities resulting from the gene knockout, and methods related to this disclosed subject matter. In addition, Applicants again note that the USPTO acknowledges that that the specification is "enabling for a method of identifying an agent that modulates an eye abnormality, the method comprising: (a) providing a transgenic mouse whose genome comprises a knockout of the gene which encodes for the native sequence PRO224 polypeptide; (b) measuring a physiological characteristic of an eye of the transgenic mouse of (a), wherein the transgenic mouse exhibits the following physiological characteristic compared with gender-matched wild-type littermates: an increased mean artery-to-vein ratio in the retinas; (c) administering a test agent to the transgenic mouse of (a); and (d) determining whether the test agent modulates said increased mean artery-to-vein ratio in the retinas of the transgenic mouse, whereby an agent which is determined to modulate said increased mean artery-to-vein ratio in the retinas of the transgenic mouse is identified" (pages 7-8 of the instant Office action, emphasis in the original).

Accordingly, Applicants respectfully submit that the rejections of claims 272, 273, 280-284, and 291 for alleged lack of enablement are overcome.

CONCLUSION

Applicants believe that the present application is in *prima facie* condition for allowance; accordingly, speedy notice of their allowance is respectfully requested.

Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **50-2387** (referencing Attorney's **Docket No. GNE-5201 R1 (25130-055)**.

Respectfully submitted,

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